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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/215,163	12/18/98	STINSON J	04995.0032-0

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FINNEGAN HENDERSON FARABOW
GARRETT & DUNNER
1300 I STREET NW
WASHINGTON DC 20005-3315

EXAMINER	
GRASER, J	
ART UNIT	**PAPER NUMBER**
1645	10

DATE MAILED: 12/14/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/215,163	Stinson et al.
Examiner	**Group Art Unit**
Graser, Jennifer	1645

☒ Responsive to communication(s) filed on *Amendment A, Paper No. 9* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-31* is/are pending in the application.

Of the above, claim(s) *3-12, 21, 22, 24-28, 30, and 31* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 2, 13-20, 23, and 29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

1. Acknowledgment and entry of the Response to Office Action submitted 10/5/2000, Paper No. 9/A is made. Claims 1, 2, 13-20, 23 and 29 are currently under examination. Please note that the Examiner of Record has changed from Verlene Ryan to Jennifer Graser.

Claim Rejections - 35 USC § 112

2. Claims 1, 2, 13-20, 23 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 fails to adequately describe and set forth the inventive concept. There are several different Shiga toxin proteins. The claims should specify which Shiga toxin protein the claimed humanized monoclonal antibody is binding to, i.e., Shiga toxin Type 2.

Claim 2 is vague and indefinite because the claim states that the humanized monoclonal antibody has the "same binding specificity as the antibody selected from the group consisting of...". Is this antibody different from the recited deposited antibodies? If so, it would not have the "same binding specificity". The claim should be amended to recite that the monoclonal antibody is selected from the group consisting of the deposited monoclonal antibodies and not something "with the same binding specificity".

Claims 13, 16 and 19 are vague and indefinite because it is unclear what is encompassed by a Shiga toxin type 2 "variants". The term variants is vague and confusing with respect to the protein it represents. How are these toxins variant?

Claim 14 recites the limitation "the mouse". There is insufficient antecedent basis for this limitation in the claim.

Claim 16 should be amended to delete the phrase "Figure 6" and the paranthetical. It is not necessary to have both the Figure and sequence identifiers in the claim. The PTO prefers to have the sequence referred to by its sequence identifier only. Appropriate correction is requested. Additionally, the phrase "at least a part of" is vague and indefinite and can read on as little as one amino acid. The metes and bounds of the invention as claimed can therefore not be understood.

Claim 19 should be amended to delete the phrase "Figure 6" and the paranthetical. It is not necessary to have both the Figure and sequence identifiers in the claim. The PTO prefers to have the sequence referred to by its sequence identifier only. Appropriate correction is requested. Additionally, the phrase "at least a part of" is vague and indefinite and can read on as little as one amino acid. The metes and bounds of the invention as claimed can therefore not be understood.

Claim 20 needs a period at the end of the claim. Additionally, the term "variants" is vague and confusing as set forth above. Additionally, the phrase "at least a part of" is vague and indefinite and can read on as little as one amino acid. The metes and bounds of the invention as claimed can therefore not be understood. Lastly, this claim is confusing because it recites a variable region containing at least part of the CDR sequences as set forth in Figure 6, but then list

the CDR sequences. The claim should either recite the sequences set forth in Figure 6 or the ones "located as follows: ". To include 2 different references to the same CDR sequences is vague and confusing.

Claims 23 and 29 are vague and indefinite due to the phrase "or fragment or derivative thereof". The term "derivative" does not provide the character or properties from the source that are to be retained in the final product, e.g., paper is derived from wood but is very different from wood. Additionally, the terms "derivative" and "fragment" imply no functionality, i.e, their is no epitope binding region retained. Further, the terms read on as little as one amino acid. Appropriate correction is required.

Claim Rejections - 35 USC § 112- Deposit Requirement

3. Claims 1, 2, 13-20, 23 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification lacks complete deposit information for the claimed monoclonal antibodies. Because it is not clear that the properties of the monoclonal antibodies are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the best mode disclosed by the specification requires the use of the plasmids, a suitable deposit for patent purposes is required. Accordingly, filing of evidence of the reproducible

production plasmids, one of ordinary skill in the art could be assured to the ability to practice the invention as claimed. Exact replication of the plasmids is an unpredictable event.

If the deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of the deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.. Amendment of the specification to recite the date of the deposit and the complete name and full street address of the depository is required.

If the deposits **have not** been made under the provisions of the Budapest Treaty, **then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:**

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become non-viable or non-replicable.

In addition, a deposit of the biological material that is capable of self-replication either directly or indirectly must be viable at the time of the deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1)The name and address of the depository;

2)The name and address of the depositor;

3)The date of deposit;

4)The identity of the deposit and the accession number given by the depository;

5)The date of the viability test;

6)The procedures used to obtain a sample if the test is not done by the depository; and

7)A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

Response to Applicants' Argument concerning deposit requirement:

Applicants have argued that the hybridoma cell lines are known and readily available to the public and therefore a deposit is not necessary. This has been fully and carefully considered but is not deemed persuasive. According to prior art references, monoclonal antibodies can be readily produced; however, the total characterization of a monoclonal antibody is a long and complex procedure which varies widely with the intended use of the antibody. A general point is that if a single hybridoma has been produced and is intended for a specific function it is unlikely that the antibody produced will have all the required characteristics (Campbell, Laboratory Techniques, Vol. 13, 1984). While the specification provides enough information for one of ordinary skill in

the art to produce hybridoma cell lines secreting antibodies with the same or similar properties as monoclonal antibodies 13C4, 11E10, humanized 13C4, reproduction of an identical cell line and antibody is an extremely unpredictable event, and because the specification lacks complete deposit information for the deposit of the hybridoma cell line(s) secreting these monoclonal antibodies and, it does not appear that these monoclonal antibodiesare known and publicly available or can be reproducibly isolated from nature without undue experimentation and because certain of the claims specifically require the use of monoclonal antibodies 11E10, 13C4 and humanized 13C4, a suitable deposit of the hybridoma cell lines for patent purpose is required.

Applicants further argue that the Budapest Treaty is not necessary with their deposit. They further argue that they have enclosed order forms from the ATCC on-line catalog for the 11E10 and 13C4 hybridoma cell lines. This argument has been considered; however it is not deemed persuasive. While deposit under Budapest Treaty is not necessary, for deposits not made under the Budapest Treaty, as set forth above, **then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:**

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of the deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become non-viable or non-replicable.

In addition, a deposit of the biological material that is capable of self-replication either directly or indirectly must be viable at the time of the deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

1)The name and address of the depository;
2)The name and address of the depositor;
3)The date of deposit;
4)The identity of the deposit and the accession number given by the depository;
5)The date of the viability test;
6)The procedures used to obtain a sample if the test is not done by the depository; and
7)A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Claim Rejections - 35 USC § 112

4. Claims 1, 13-20, 23 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized monoclonal antibody which binds to Shiga toxin I, does not reasonably provide enablement for 'humanized monoclonal antibodies which bind to Shiga toxin type 1 variants' or 'fragments or derivatives' from a humanized monoclonal antibody which binds to Shiga toxin type 1, nor does the specification enabled for humanized monoclonal antibodies wherein 'at least part of' the variable region is from SEQ ID NO:42 and SEQ ID NO:43. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 23 and 29 recite fragments or derivatives from a humanized monoclonal antibody yet provide no functional and/or size limitation. These fragments and derivatives do not have to have a use, i.e., they may not necessarily bind Shiga Toxin 1. The specification further discloses humanized monoclonal antibodies which will bind to Shiga type I toxin and humanized monoclonal antibodies which contain "at least part of the variable region from SEQ ID NO:42 and 43. The specification states that substitutions, additions, or deletions may be made to the sequence encoding the antibody; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the antibody to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the

position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. The changes allowed for in the claims could cause a detrimental effect to the antibody to be produced and could cause total negation of any epitopes which could correctly bind Shiga Toxin I. It is unclear that an immunogenic epitope binding region would be retained in the fragments and derivatives. Additionally, the specification has not adequately set forth the location of immunoprotective epitopes. The specification sets forth nothing less than a humanized monoclonal antibody which can bind Shiga Toxin I as exemplified the deposits recited in claim 2. Selective point mutation to one key antigen residue could, in practical terms, eliminate the ability of the antibody to recognize the Shiga I toxin. If the range of decreased binding ability after single point mutation of an antibody varies, one could expect point mutations in the antibody to cause varying degrees of loss of binding, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes could result in a complete loss of binding. An antibody having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antibody that is precipitously or progressively unrecognizable and unable to bind to the Shiga toxin. Thus, antibodies of different levels of homology may not recognize by the native Shiga Toxin I. Given the lack of guidance contained in

the specification and the unpredictability for determining acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation..

Claim Rejections - 35 USC § 103

5. Claims 1, 2, 13-20, 23 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Speirs et al (Can. J. Microbiol., 1991, 37: 650-653) or O'Brien et al (US 5,747,272) in view of Shitara et al (US 5,866,692).

Speirs et al teach the 11E10 monoclonal antibody which binds to shiga-toxin II. See especially abstract, page 651, first column).

O'Brien et al also teach the 11E10 monoclonal antibody of the IgG1 subclass with a kappa light chain. See especially column 4, lines 38-58.

Shitara et al teach a method of producing humanized chimera antibodies. Humanized chimera does not cause formation of anti-mouse immunoglobulin antibody in the body of the patient and therefore side effects are reduced. See abstract and column 1, lines 10-48).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to synthesize and express the humanized chimera antibody which binds to the shiga-like toxin type II. One of ordinary skill in the art would have been motivated to humanize the monoclonal antibodies taught by Speirs and O'Brien because doing so would avoid the side effects caused by anti-mouse immunoglobulin antibody when monoclonal antibody is administered, yet it would still maintain an effective therapeutic effect. The humanization of a

monoclonal antibody which is already known in the prior art, particularly one directed to a human pathogen, would have been obvious at the time the invention was made since it was a common procedure to allow for the passive immunization against human pathogens while avoiding serious side effects.

Response to Applicants' arguments:

Applicants have argued that both O'Brien and Speirs rely on their monoclonal antibodies. This has been fully considered but is not deemed persuasive. This demonstrates that monoclonal antibodies to Shiga Toxin 1 were well known. To humanize them would have been obvious. The humanization of a monoclonal antibody which is already known in the prior art, particularly one directed to a human pathogen, would have been obvious at the time the invention was made since it was a common procedure to allow for the passive immunization against human pathogens while avoiding serious side effects.

Applicants further argue that O'Brien and Speirs are directed to detection methods and neither reference mentions treatment of patients. This argument has been fully and carefully considered but is not deemed persuasive. The instant claims are not drawn to methods of treating, but merely to the humanized antibodies. Applicants further argue that one of ordinary skill in the art would not have been motivated to adapt detection antibodies for pharmaceutical use. This has been carefully considered but is not deemed persuasive. The humanization of a monoclonal antibody which is already known in the prior art, particularly one directed to a human pathogen, would have been obvious at the time the invention was made since it was a common

procedure to allow for the passive immunization against human pathogens while avoiding serious side effects. One of ordinary skill in the art would have recognized the potential for passive immunization techniques of a monoclonal antibody directed to a common human pathogen. Lastly, Applicants state that if the existence of motivation to combine these references existed it would, at best, lead to a motivation to try the combination. This has been fully and carefully considered but is not deemed persuasive. One of ordinary skill in the art would encounter no obstacles or inherent difficulties when faced with the humanizing of well known monoclonal antibodies. This is a common procedure and would not have amounted to "a motivation to try". Applicants arguments with regard to their showing that methods of administering the humanized monoclonal antibody that binds to Shiga toxin protein protects mice from lethal oral dose of toxigenic *E.coli* is not commensurate in scope with the claimed invention which is drawn to a product, not a method.

Status of Claims

6. No claims are allowed.

7. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Jennifer Graser
Primary Examiner 4/12/00
Art Unit 1645